Serial Number: 09/549,858
Group Art Unit: 1614
Examiner: Jones, D.

The Office Action states that "Oishi *et al.* teach of stable anti-ulcerative preparations, which contain an amino acid, namely glycine, and a benzimidazole compound...The claims differ from the reference by reciting a more limited genus than the reference." Applicants respectfully submit that this is not the case.

Claims 1, 2 and 4 of the JP '225 Application are directed to a preparation containing stabilized anti-ulcer agent. The specification goes on to define the pH of the resulting preparation to have an alkaline value of 8-9. Further, the JP '225 application is *concerned only with oral dosage forms* whereas the Applicants demonstrate the stabilization of the anti-ulcer compounds for *intravenous administration*. With respect to JP '225, it states on page 3 of the translation:

> the stability of these benzimidazole compounds is poor, and they are unstable with respect to temperature, moisture and light when in solid form. In addition, the substances rapidly decompose and become extremely discolored in aqueous solutions that are acidic or neutral. Moreover, in preparations such as tablets, fine particles, granules, capsules, and powders, the substances are affected by the other components in the preparation formula, and are thus rendered unstable. As a result, the content of compound decreases over time, and discoloration occurs. Furthermore, when the compounds are coated in the form of tablets or granules in these preparations, their compatibility with enteric bases (e.g. cellulose acetate phthalate, hydroxyproplylmethylcellulose phthalate, hydroxy-proplylmethylcellulose acetate succinate, polyvinyl acetate phthalate, methacrylic-acrylic acid copolymer) is poor, and thus a decrease in content and discoloration occur. When manufacturing ***oral preparations of benzimidazole compounds*** of this type, even if it is not necessary to blend the compounds with other components or to coat them with enteric base, it is difficult to form a preparation due to the detrimental effects acting on stability described above. Consequently, when formulating these compounds into ***oral dosage forms***, it is necessary to sufficiently stabilize the compounds.

Clearly, the JP '225 does not address the problems of an aqueous solution suitable for intravenous administration.

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The instant application, in marked contrast, is primarily concerned with the aqueous reconstitution of said anti-ulcerative compounds. As stated in the instant application at page 2, lines 4-17:

> It is desirable when preparing *reconstituted solutions of such anti-ulcerative compounds* that are suitable *for intravenous administration*, that the *solubilized compounds* exhibit physical and chemical stability for at least between about 6 and about 12 hours at room temperature. It has been found by the present inventors that anti-ulcerative compounds such as Compound 1 and the compounds described general formula I below discolor when they are *reconstituted, i.e., dissolved, in aqueous solutions, particularly in solutions suitable for intravenous administration,* e.g., 5% dextrose or 0.9% saline. Such solutions quickly turn yellow to yellow-brown. (Italics added)
>
> The compounds of the present invention have been determined to be more potent H^+/K^+-ATPase inhibitors than omeprazole sodium. However, in order *to provide clinically useful pharmaceutical formulations of the compounds disclosed herein for intravenous administration,* it is first necessary to provide formulations for lyophilization and intravenous administration that do not degrade physically, chemically, and /or demonstrate a change on color.

The instant application further states at page 4, lines 9-19:

> It has now been *surprisingly and unexpectedly* discovered that if lyophilized compounds of general formula I below are reconstituted in isotonic solutions suitable for intravenous administration, such as 5% dextrose or 0.9% sodium chloride, that have been brought to a pH of between about 9 and about 12, preferably between about pH 10 and 11, by a glycine-sodium hydroxide buffer, such formulations are chemically and physically stable, and do not significantly change color, for at least between about 6 hours and about 12 hours at room temperature. It was also discovered that the use of glycine buffers with a pH of between about 9 and about 12, preferably between about pH 10 and pH 11, is beneficial in preparing lyophilized samples of the compound of the invention (italics added).

Not only have the inventors addressed the issue of the requisite *aqueous stability* of these compounds inherent for *intravenous administration* and succeeded in producing a *novel* solution,

they have also determined a *novel* method for the stabilization of lyophilized samples of the compounds of general formula I as stated in the instant patent application (see page 13, lines 16-18).

Accordingly, Applicants submit that the instant claimed invention is not taught by Oishi *et al.* Applicants therefore request that the Examiner reconsider and withdraw this rejection.

II. Rejection under 35 U.S.C. § 103(a) as Unpatentable over U.S. 5,536,735

Claims 1-23 are rejected under 35 U.S. C. § 103(a) as unpatentable over U.S. 5,536,735 (" '735" patent) ("Takechi *et al.*"). Applicants respectfully traverse this rejection.

The Office Action states that Takechi *et al.* teach a stable injectable preparation, which has anti-ulcerative activity and that contains an amino acid, namely glycine, and a benzimidazole compound. The Office Action goes on to list 5 places ("see columns 1,2,5,6 and column 8") in the specification where this is apparently cited. Applicants respectfully submit that this is not the case.

The specification of the '735 patent states in the Background of the Invention at column 1, line 34, "but it has not been reported that nicotinamide is used with the benzimidazole compounds for injectable solution." And also in the Summary of the Invention at column 1, lines 64-67, "According to this invention, there is provided: 1) A pharmaceutical composition which comprises a benzimidazole compound having antiulcer activity and a water-soluble carboxylic acid amide..." Clearly, the '735 patent is teaching the stabilization of benzimidazoles using nicotinamide.

The '735 patent goes on to describe the lyophilzation of benzimidazoles at column 8, lines 37 to 48:

> Where lyophilization is carried out, a form regulator may be added to an aqueous solution of the benzimidazole compound having antiulcer activity for the purpose of improving the morphology of the lyophilizate. The form regulator mentioned above includes various sugars (e.g. sugar alcohols such as mannitol, xylitol, inositol, sorbitol, etc., hexose-based disaccharides such as maltose,

> sucrose, lactose, etc., and monosaccharides such as glucose), neutral amino acids (e.g. glycine, alanine, proline, valine, methionine, etc.) and alkali metal salts of succinic acid (e.g. sodium succinate, etc.). Preferred, among these form regulators, are sugars. Particularly, sugar alcohols are preferred.

Here, it seems clear that the preferred "form regulator" for the lyophilzation of the benzimidazole "are sugars, [p]articularly, sugar alcohols are preferred." Further, glycine is first mentioned here in the specification amongst a long list of possible "form regulators" and is not listed as a "preferred" one. Hence, one skilled in the art would not assume that glycine is the preferred "form regulator" for improving the "morphology of the lyophilizate."

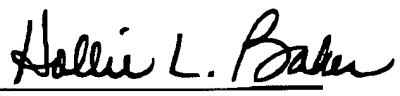
Further, it is noteworthy that within the 10 claims of the '735 patent, glycine is not listed as a preferred additive to the stabilization of the benzimidazole, rather the focus is on the nicotinamide as the stabilizer of the benzimidazole.

Accordingly, Applicants submit that the instant claimed invention is not taught by Takechi *et al.* Applicants therefore request that the Examiner reconsider and withdraw this rejection.

III. Conclusion

Applicants respectfully submit that all the bases for rejection of the pending claims are now moot. The Examiner is requested to reconsider the rejections and to withdraw them and to pass this case to issuance.

Respectfully submitted,



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Date: **September 24, 2002**

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